

# WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLIS	HED 1	JNDER THE PATENT COOPERATION TREATY (PCT)
(51) International Patent Classification 6:		(11) International Publication Number: WO 96/35443
A61K 38/00, 38/02, C07K 5/00, 7/00, 17/00	A1	(43) International Publication Date: 14 November 1996 (14.11.96)
(21) International Application Number: PCT/US		DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(22) International Filing Date: 5 April 1996	(05.04.9	6)
(30) Priority Data: 08/440,504 12 May 1995 (12.05.95)	ι	Published With international search report.
(71) Applicant: SANGSTAT MEDICAL CORPO [US/US]; 1505B Adams Drive, Menlo Park, C (US).	DRATIO	N 25
(72) Inventor: BUELOW, Roland; 2747 Ross Road, Palo 94303 (US).	Alto, Ć	A
(74) Agents: ROWLAND, Bertram, I. et al.; Flehr, Hohb. Albritton & Herbert, Suite 3400, 4 Embarcadero Co Francisco, CA 94111-4187 (US).		
		·
• •	,	
(54) Title: TREATMENT FOR INHIBITING THE PROC	GRESSI	ON OF AUTOIMMUNE DISEASE
(57) Abstract		
The progression of autoimmune disease is inhibited $\alpha$ 1-domains. These fragments include the amino acids bet significantly decreased by the subject treatment.	by the a	dministration of peptides having the sequences of MHC Class I antigen sitions 70 and 91 of the MHC Class I antigens. The onset of IDDM is
·		•
		÷
•		

# FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austrila GE Georgia MX Mexico AU Australia GN Guinea NE Niger BB Barbados GR Greece NL Netherlands BE Belgium HU Hungary NO Novovay BF Burkina Paso IE heland NZ New Zealand BG Bulgaria IT haly PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Slovenia CI Côte d'Ivolre LI Llechtenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CC Czech Republic LU Luxembourg TG Togo DK Gemeny LV Latvia TJ Tajikistan DK Denmark MC Monaco TT Trinidad and Tobago ES Spain MG Madagasacar UG Uganda FR France MN Monagolia UZ Uzbekistan	AM	Armenia	GB	United Kingdom	MW	Malawi
AU Australia GN Gumea NE Niger BB Barbados GR Greece NL Netherlands BE Belgium HU Hungary NO Norway BF Burkina Faso IE heland NZ New Zealand BG Bulgaria IT Italy PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Stovenla CI Cote d'Ivolre LI Libethastein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Libetria SZ Swaziland CZ Czechoslovakia LT Libuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistam DK Demnark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FF Finland ML Mali US United States of Ame FFR France	АT	Austria	GE			
BB Barbados GR Greece NL Netherlands BE Belgium HU Hungary NO Norway BF Burkina Paso IE heland NZ New Zealand BG Bulgaria IT haly PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singapore CH Switzerland KZ Kazakhstan SI Slovenla CI Côte d'Ivoire LI Liechtenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Lithuania TD Chad CCZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Demuark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ulrraine ES Spain MG Madagasacar UG Uganda FR France MN Monagolia UZ Uzbekistan		Australia	GN	Guinea		
BE Belgium HU Hungary NO Norway BF Burkina Paso IE heland NZ New Zealand BG Bulgaria IT haly PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazaktstan SI Slovenia CI Côte d'Ivoire LI Liechtenstein SK Slovakita CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Lithuania TD Chad CCZ Czech Republic LU Luxembourg TC Togo DE Germany LV Lavvia TJ Tajikistan DK Dennark MC Monaco TT Trinidad and Tobago EB Estonia MD Republic of Moldova UA Urraine ES Spain MG Madagasacar UG Uganda FR France MN Monagolia UZ Usbeitstan OIL SU Lukistan On Monagolia  UZ Uzbeitstan UZ Uzbeitstan US United States of Ame		Barbados	GR	Стессе		
BF Burkinn Pasco IE hreland NZ New Zealand BG Bulgaria IT haly PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Slovenla CI Côte d'Ivoire LI Liecheastein SK Slovakha CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libhuania TD Chad CCZ Czech Republic LU Luxembourg TG Togo DE Germany LV Larvia TJ Tajikistan DK Dennark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagaster UG Uganda FF France MN Monagolia UZ Uzbekistan	BE	Belgium	HU	Honeary		
BG Bulgaria IT haly PL Poland BJ Benin JP Japan PT Portugal BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Stovenla CI Cote d'Ivolre LI Liechenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Denmark MC Monaco TT Trinidad and Tobago RE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FR France MN Monagolia UZ Uzbekistan		Burkina Faso	IE			
BJ Benin JP Japan PT Portugal BR Brazil KE Keaya RO Romania BY Belarus KG Kyrgystam RU Russian Federation CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singapore CH Switzerland KZ Kazakhstam SI Slovenla CI Côte d'Ivolre LI Liechtenstein SK Slovakha CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Lihaania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistam DK Dennark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FR France MN Monagolia UZ Uzbekistan		Bulgaria	IT	Italy		
BR Brazil KE Kenya RO Romania BY Belarus KG Kyrgystan RU Russian Federation CA Canada RP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Slovenla CI Côte d'Ivolre LI Liechtenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libhuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Denmark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FF Finland MI Mali US United States of Ame FF France MN Monagolia UZ Uzbeistan	BJ	Benin	. JP			
BY Belaus KG Kyrgystan RU Russian Federarioo CA Canada KP Democratic People's Republic SD Sudan CF Central African Republic of Korea SE Sweden CG Congo KR Republic of Korea SG Singupore CH Switzerland KZ Kazakhstan SI Slovenla CI Cote d'Ivolre LI Liechtenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Lihuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Demnark MC Monaco TT Trinidad and Tobago RE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FF Finland ML Mali US United States of Ame FF France MN Mongolia UZ Uzbekistan	BR	Brazil	KÆ			
CA Canada CF Central African Republic CF Central African Republic CG Congo CH Switzerland CI Côte d'Ivoire LI Liechtenstein CN China LR Liberia CS Czechoslovakia LT Lithuania CZ Czech Republic LU Luxembourg DE Germany LV Latvia DE Germany LV Latvia DE Estonia ES Spain MG Madagascar MG Madagascar MG Mali MIL Mali MOngolia LV Liberland MS Mongolia LV Uzbekistan  Nodan  Notada SE Swaden SE Sweden SE Sweden SE Swaden SE Swaden SE Swaden SE Swaden SE Swazikan SI Slovakia SI Slovakia SN Senegal Chad Cz Czechoslovakia LT Lithuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan TT Trinidad and Tobago UG Uganda FF Finland MIL Mali US United States of Ame FF France	BY	Belarus				
CF Central African Republic  CG Congo  KR Republic of Korea  SE Sweden  SE Sp	CA	Canada	KP			
CG Congo KR Republic of Korea SG Singapore CH Switzerland KZ Kazakhstan SI Slovenla CI Côte d'Ivolre LI Llechenstein SK Slovakia CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libriania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Larvia TJ Tajikistan DK Dennark MC Monaco TT Trinidad and Tobago RE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagasacar UG Uganda FF Finland ML Mali US United States of Ame FF France MN Mongolia UZ Uzbekistan	CF	Central African Republic				
CH Switzerland KZ Kazakhstan SI Slovenla CI Côte d'Ivolre LI Llechtenstein SK Slovakla CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libhuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Denmark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagasacar UG Uganda FF Finland ML Mali US United States of Ame FF France MN Mongolia UZ Uzbekistan	CG	Congo .	KR			
CJ         Côte d'Ivolre         LI         Liechteristein         SK         Slovakia           CM         Cameroon         LK         Sri Lanka         SN         Senegal           CN         China         LR         Liberia         SZ         Swaziland           CS         Czechoslovakia         LT         Libuania         TD         Chad           CZ         Czech Republic         LU         Luxembourg         TG         Togo           DE         Germany         LV         Lavia         TJ         Tajikistan           DK         Denmark         MC         Monaco         TT         Trinidad and Tobago           EE         Estonia         MD         Republic of Moldova         UA         Ukraine           ES         Spain         MG         Madagascar         UG         Uganda           FI         Finland         ML         Mali         US         United States of Ame           FR         Prance         MN         Mongolia         UZ         Uzbekistan	CH	Switzerland	KZ.			
CM Cameroon LK Sri Lanka SN Senegal CN China LR Liberia SZ Swaziland CS Czechoslovakia LT Libhuania TD Chad CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Deumark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ulraine ES Spain MG Madagascar UG Uganda FT Finland ML Mdii US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	CI	Côte d'Ivoire				
CN China I.R Liberia SZ Swarland  CS Czechoslovakia I.T Libhuania TD Chad  CZ Czech Republic LU Luxembourg TG Togo  DE Germany L.V Larvia TJ Tajikistan  DK Dennark MC Monaco TT Trinidad and Tobago  EE Estonia MD Republic of Moldova UA Ukraine  ES Spain MG Madagascar UG Uganda  FI Finland ML Mali US United States of Ame  FR Prance MN Mongolia UZ Uzbekistan	CM	Cameroon				
CS Czechoslovakia LT Lithuania TD Chad  CZ Czech Republic LU Luxembourg TG Togo  DE Germany LV Latvia TJ Tajikistan  DK Denmark MC Monaco TT Trinidad and Tobago  EE Estonia MD Republic of Moldova UA Ukraine  ES Spain MG Madagascar UG Uganda  FI Finland ML Mali US United States of Ame  FR France MN Mongolia UZ Uzbekistan	CN	China				
CZ Czech Republic LU Luxembourg TG Togo DE Germany LV Latvia TJ Tajikistan DK Denmark MC Monaco TT Trimidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FI Finland ML Mali US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	CS	Czechoslovakia				
DE Germany LV Latvia TJ Tajikistam DK Deumark MC Monaco TT Trinidad and Tobago EE Estonia MD Republic of Moldova UA Ukraine ES Spain MG Madagascar UG Uganda FI Finland ML Mali US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	CZ			<del></del>		
DK         Denmark         MC         Monaco         TT         Trinidad and Tobago           EE         Estonia         MD         Republic of Moldova         UA         Ukraine           ES         Spain         MG         Madagascar         UG         Uganda           FI         Finland         ML         Mali         US         United States of Ame           FR         Prance         MN         Mongolia         UZ         Uzbekistan	DE					
EE Estonia MD Republic of Moldova UA Urraine ES Spain MG Madagascar UG Uganda FI Finland ML Mali US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	DK					
ES Spain MG Madagascar UG Uganda FI Finland ML Mali US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	EE	Estonia				
FI Finland ML Mali US United States of Ame FR Prance MN Mongolia UZ Uzbekistan	ES	Spain				
FR France MN Mongolia UZ Uzbekistan	FI					
Will Mongona UZ Uzbekistan	FR	France				
	GA	Gabon	MR			
MR Mauritania VN Vict Nam			MIR	Maurania	VN	Vict Nam

# TREATMENT FOR INHIBITING THE PROGRESSION OF AUTOIMMUNE DISEASE

#### INTRODUCTION

#### 5 Technical Field

The field of this invention is the regulation of autoimmune disease using peptide fragments.

#### **Background**

The complex immune system of mammals and birds must achieve a delicate balance, where pathogens are recognized and eliminated, but host cells are safe from immune destruction. Subtle environmental and genetic factors can disrupt this balance, sometimes resulting in autoimmune disease. Attack by autologous cells of the immune system can be directed to a number of different targets, and have been correlated with a large number of disorders. Among them are neural diseases, such as multiple sclerosis and myasthenia gravis, diseases of the joints, such as rheumatoid arthritis, attacks on nucleic acids, as observed with systemic lupus erythematosus and such other diseases as psoriasis, insulin dependent diabetes mellitus (IDDM), Sjogren's disease, and thyroid disease. These diseases have a variety of symptoms, varying from minor and irritating to life-threatening.

Despite the extensive research efforts that have been involved with elucidating the basis for these diseases, the diseases for the most part have been recalcitrant to an understanding of their etiology in the development of therapeutic modes. Many of the diseases are believed to be associated with lymphocytic involvement, which can result in attack and degradation of proteins, cytotoxicity, and the like.

Insulin dependent diabetes mellitus, IDDM, has been linked to specific alleles of Class II MHC antigens. In particular, associations have been found in the Caucasian

population with the allele DQB1\*0302 (DQ3.2). This evidence has suggested that there is a link between the activity of CD4\* T lymphocytes and the onset of IDDM. The delay in onset of disease achieved by administration of cyclosporin A, which specifically inhibits CD4\* T cells, has supported this view.

The NOD mouse spontaneously develops a disease closely resembling IDDM in histology and range of autoimmune responses, which disease is also linked to loci of MHC Class II antigens. Under appropriate circumstances, transfer of T cells can induce early disease in young NOD mice. In the course of disease, the loss of  $\beta$  cells in the pancreatic islets of Langerhans is preceded by a peri-islet infiltration of CD4<sup>+</sup> T cells, followed by CD8<sup>+</sup> cells and macrophages. Macrophages are also important mediators of the tissue damage.

The role of T-cell subsets in the pathogenesis of IDDM is a matter of controversy. Conflicting data have been published. In some experiments it has been shown that islet destruction can be mediated by CD4<sup>+</sup> T cells alone. Others have reported that, in the absence of Class I MHC antigens, there was no development of disease.

There is a need to develop therapies which can aid a patient by diminishing the detrimental effects of an autoimmune disease or by substantially inhibiting its course of action. By intervening in the effects of T lymphocyte effector functions, there may be ways to protect the host from autoimmune diseases.

### 20 Relevant Literature

5

10

25

The sequences of known HLA and H-2 alleles may be found in Kabat et al. (1991) Sequences of Proteins of Immunological Interest, N.I.H. publication no. 91-3242, vol. I, pp. 738-740, 761, 770-771, 779-780, 788-789 and 802-804. The composition and uses of such peptides are further described in International application PCT/US93/01758. Stagsted et al. (1990) Cell 62:297-307 disclose the regulation of insulin receptor functions by a peptide derived from an MHC Class I peptide. The peptides are further disclosed in International application PCT/US89/00876.

Nisco et al. (1994) <u>J. Immunol.</u> 152:3786 demonstrate the induction of allograft tolerance in rats by an HLA Class I derived peptide and cyclosporin A. Similar tolerance in mice was shown by Beulow et al. (1995) <u>Transplantation</u> 59:455-460. Prolongation of allogeneic heart graft survival in rats by administration of a peptide from the  $\alpha1$  helix of the first domain of HLA-B7 is described in Cuturi et al. (1995) <u>Transplantation</u>

59:661-669. Immunomodulation by soluble Class I molecules is reviewed in Beulow et al. (1995) Transplantation 59:649-654.

The role of CD8+ T cells in the pathogenesis of IDDM is discussed in Bradley et al. (1992) <u>Diabetes</u> 41:1603-1608. Katz et al. (1993) <u>Eur. J. Immunol.</u> 23:3358-3360 disclose the requirement for MHC Class I molecules in the development of insulitis in NOD mice. Miyazaki et al. (1992) <u>P.N.A.S.</u> 89:9519-9523 demonstrate the prevention of insulitis by expression of MHC L molecules.

Treatment of diabetes with peptides of MHC Class II molecules is discussed in L. Adorini (1992) <u>I. Autoimmunity</u> 5:73-81; Hurtenbach *et al.* (1993) <u>I. Exp. Med.</u> 177:1499-1504; and Lock *et al.* (1991) <u>Sem. Immunol.</u> 3:247-255.

The progression of disease for IDDM is reviewed in Foulis et al. (1986) Diabetologia 29:267-274; Caillat-Zucman et al. (1992) J. Clin. Invest. 90:2242-2250; Vandewalle (1993) Diabetologia 36:1155-1162; and Karjalainen et al. (1989) N. Engl. J. Med. 320:881-886. The association of human IDDM with various genetic markers is discussed in Davies et al. (1994) Nature 371:130-136.

#### SUMMARY OF THE INVENTION

Methods and compositions for inhibiting the progression of autoimmune disease are provided, based on the administration of peptides having a sequence at least in part of an MHC Class I antigen  $\alpha$ 1-domain. These fragments include the sequence of amino acids between positions 70 to 91 of the MHC Class I antigens and are used to modulate T cell mediated attack on autologous target cells.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph depicting the effect of peptides administered by intravenous injection on the incidence of IDDM in female NOD mice.

25

30

Figure 2 is a graph depicting the effect of peptides administered by intraperitoneal injection.

#### DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The adverse effects of autoimmune disease are lessened by the administration of peptides having the sequence of MHC Class I antigen  $\alpha 1$ -domains. These fragments

include the amino acids between positions 70 and 91 of the MHC Class I antigens. For a given locus, the amino acid sequence of this region has several invariant residues, and is otherwise generally conservative among different alleles. Between related species, *i.e.* among mammals, there are also sequence similarities in this region. Class I MHC antigens of interest include the human HLA-A, -B, -C, -E and -G, and murine H-2K and H-2D, and derivatives thereof.

A pharmaceutically acceptable formulation of the subject peptides is administered to a host suffering from an autoimmune disease. The data indicates that the treatment acts by reducing the severity of cytotoxic T lymphocyte mediated attack on autologous tissue. Generally the cytotoxic T lymphocytes will be CD8<sup>+</sup>. The effect is to spare the function of the autologous tissue which is the target of the autoreactive T lymphocytes. In addition, there may be a reduction in the inflammation, swelling, release of cytokines, perforins, granzymes, etc. which are associated with T cell activation.

One group of therapeutic compositions comprise oligopeptides of at least 6 amino acids comprising the tripeptide or triad (SEQ ID NO:1) TYR-TYR-TRP (YYW), preferably the tetrapeptide (SEQ ID NO:2) ARG-TRY-TYR-TRP (RYYW). At the N terminus of the tripeptide or tetrapeptide, there will usually be at least about 4 amino acids, more usually at least about 5 amino acids, where for the most part, the sequence of amino acids will be the sequence of the Class I HLA-B  $\alpha_1$  domain, residues 80 to 86, more usually 78 to 86, frequently 75 to 86, or the equivalent thereof of other species, e.g. mouse, rat, etc. In some cases the sequence of amino acids will extend beyond residues 75 to 83, although as the oligopeptide is extended, an increasing number of substitutions from the natural sequences are permissible. The C terminus of the tripeptide or tetrapeptide may also be extended, usually by not more than 5 amino acids, more usually by not more than 3 amino acids, frequently not more than 1 amino acid.

For the most part, the oligopeptides will have at least 6, usually at least 8, amino acids and come within the following formula:

```
aa<sup>70</sup> aa<sup>71</sup> Q aa<sup>73</sup> aa<sup>74</sup> R aa<sup>76</sup> aa<sup>77</sup> L aa<sup>79</sup> aa<sup>80</sup> aa<sup>81</sup> aa<sup>82</sup> aa<sup>83</sup> Y Y aa<sup>86</sup> aa<sup>87</sup> aa<sup>88</sup> aa<sup>80</sup> aa<sup>91</sup>.

Wherein:
```

aa<sup>70</sup> is Q, H, S, N or K;

aa<sup>71</sup> is an aliphatic neutral amino acid, including S, A and T;

aa<sup>73</sup> is T or A;

aa<sup>14</sup> is D, Y or H; aa<sup>16</sup> is E or V; aa<sup>17</sup> is D, S or N; aa<sup>18</sup> is R or G;

10

20

aa<sup>20</sup> is T, I, N or an aromatic amino acid, e.g., F, W or Y;
aa<sup>21</sup> is an aliphatic non-polar amino acid including L or A;
aa<sup>22</sup> is R, L or an aromatic amino acid, particularly L;
aa<sup>23</sup> is G or R;
aa<sup>24</sup> is W or N;

axes is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S;

aass is an aromatic amino acid or aliphatic amino acid of from 5 to 6 carbon atoms, particularly F, W, Y, L, I or V;

aa<sup>30</sup> is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S;

aa<sup>so</sup> is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S; and

aan is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S.

Desirably, for the amino acid sequence after position aa<sup>86</sup> (W), the sequence will alternate an aromatic amino acid with an aliphatic amino acid, particularly a neutral aliphatic amino acid.

Also of interest are compositions coming within the above formula, comprising the sequence from position 75 to 84.

For the most part, the peptides will be at least 6 amino acids, more usually at least 8 amino acids, frequently at least 10 amino acids and up to the entire sequence of 22 amino acids or the dimer of 44 amino acids for the active sequence. The active sequence may be bonded or non-covalently linked within a chain or as a side chain of other peptides or proteins, for a variety of purposes. The peptide may be cyclized by various methods, as

30 known in the art.

Also included in the subject compositions are oligopeptide dimers, which may be head to head, tail to tail, or head to tail. In addition, 1 or more of the amino acids may be the D-stereoisomer, up to all of the amino acids.

Compositions of particular interest have the following formula:

(SEQ ID NO:3) R V/E N/D L R I A/L L R/E Y Y W Q/D S, where the backslashes intend that either amino acid may be present at that position. The preferred compositions will have at least 8 amino acids, preferably at least about 10 amino acids. The 10 amino acids may comprise a sequence within the above formula which includes the tripeptide YYW, desirably, terminating with W. Alternatively, the 10 amino acids may comprise the sequence (SEQ ID NO:16) R V/E N/D L R I A/L L R/E Y.

For the most part, the peptides of the subject invention will employ the amino acids naturally found at the  $\alpha$ 1-domain, except as specifically indicated. While the combinations of amino acids may not be naturally found, the individual amino acid will usually be present in one or more  $\alpha$ 1 domains. One may have up to and including 2 mutations, usually not more than about 1 mutation, where the term "mutation" is intended to mean that one does not find that amino acid present at that particular position in the HLA-B  $\alpha$ 1-domain sequence, or the sequence of the analogous protein in other species, particularly mouse, excluding the tryptophan at amino acid 86 as coming within the number of mutations.

The subject peptides may be modified in a wide variety of ways. Sequence analogs may be prepared by oligopeptide synthesis using a stepwise substitution of the amino acids at each position with alanine or valine, particularly alanine. Generally the total number of amino acids substituted will not exceed 3, ranging from 1 to 3, usually 1 to 2. Methods of producing "scanning" mutatations are known in the art, and have been successfully used with a number of different peptides. Examples of protocols for scanning mutations may be found in Gustin, et al. (1993) Biotechniques 14:22; Barany (1985) Gene 37:111-23; Colicelli, et al. (1985) Mol Gen Genet 199:537-9 and Prentki, et al. (1984) Gene 29:303-13.

The peptides may be joined by covalent bonds at any convenient site along the peptide to a variety of other compounds for different purposes. Of particular interest is joining the subject peptides to another molecule by synthesis or expression of a synthetic gene where the other molecule provides for extended stability of the subject peptides when administered to a host. Various peptides may be used, such as the immunoglobulin

10

30

constant region, e.g. IgG Fc, or the peptide may be joined to a lipid or polyalkyleneoxy group, to a sugar; or to a nucleic acid. The peptide may be PEGylated, where the polyethyleneoxy group provides for enhanced lifetime in the blood stream. One can prepare these compositions by preparing or isolating a gene coding for the particular peptide or protein, and joining that gene to a DNA sequence coding for the subject peptide. The gene may be introduced into an appropriate expression vector, there being many expression vectors commercially available, whereby the gene is then expressed in an appropriate host. See, Sambrook et al., Molecular Biology: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.

The peptides may be prepared in a variety of ways. Conveniently, they can be synthesized by conventional techniques employing automatic synthesizers, such as the Beckman, Applied Biosystem Inc., or other useful peptide synthesizer apparatus, or may be synthesized manually. Alternatively, DNA sequences can be prepared that encode the particular peptide and may be cloned and expressed to provide the desired peptide. In this instance a formyl-methionine may be the first amino acid, or repetitive sequences may be cleaved to produce the individual peptides. Unnatural amino acids may also be used, particular the D-isomer of naturally occurring amino acids, or a mixture of D- and L-isomers.

The peptides may also be isolated from natural sources and purified by known techniques, including, for example, chromatography on ion exchange materials, separation by size, immunoaffinity chromatography and electrophoresis. As used herein, the term "a substantially pure preparation of peptide compound" means a preparation of the peptide that is usually greater than about 75% free of materials with which the polypeptide is naturally associated, and usually greater than about 90% free of these materials; these materials, however, exclude materials with which the peptide may be mixed in the preparation of pharmaceutical compositions. Usually, the percentages will be based upon total protein. The sequences may be modified in a variety of ways depending upon their ultimate purpose. Different N- or C- terminal groups may be introduced which allow for linking of the peptide to solid substrates or other molecules, or for cyclization.

Chemical linking may be provided to various peptides or proteins comprising convenient functionalities for bonding, such as amino groups for amide or substituted amine formation, e.g. reductive amination, thiol groups for thioether or disulfide formation,

10

15

20

30

carboxyl groups for amide formation, and the like. Of particular interest are peptides of at least 2, more usually 3 and not more than about 60 lysine groups, particularly polylysines of from about 4 to 20, usually 6 to 18 lysine units, referred to as MAP, where the subject peptides are bonded to the lysine amino groups, generally at least about 20%, more usually at least about 50%, of available amino groups, to provide a multipeptide product. Thus, when one obtains molecules having a plurality of the subject peptides where the orientation of the subject peptides is in the same direction, in effect one has a linking group to provide for tail to tail di- or oligomerization. Alternatively, other naturally occurring or synthetic peptides and proteins may be used to provide a backbone for attachment of the subject peptides at the C terminus.

The peptides will be administered to a host which is susceptible to an autoimmune disease. Of particular interest are primates, more particularly humans, but other mammals are also of interest, particularly domestic animals such as equine, bovine, ovine, feline, canine, murine, lagomorpha, and the like. The diseases of interest will be associated with T-cell mediated tissue destruction. Included are multiple sclerosis, rheumatoid arthritis, psoriasis, pemphigus vulgaris, Sjogren's disease, thyroid disease, Hashimoto's thyroiditis, myasthenia gravis, as well as many others. Of particular interest is insulin dependent diabetes mellitus (IDDM), also known as juvenile onset or Type I diabetes, associated with destruction of beta cells in the pancreatic islets of Langerhans.

The peptide composition will desirably be administered during the presymptomatic or preclinical stage of the disease, and in some cases during the symptomatic stage of the disease. Early treatment is preferable, in order to prevent the loss of function associated with autoimmune tissue damage. The presymptomatic, or preclinical stage will be defined as that period not later than when there is T cell involvement at the site of disease, e.g. islets of Langerhans, synovial tissue, thyroid gland, etc., but the loss of function is not yet severe enough to produce the clinical symptoms indicative of overt disease. T cell involvement may be evidenced by the presence of elevated numbers of T cells at the site of disease, the presence of T cells specific for autoantigens, the release of perforins and granzymes at the site of disease, response to immunosuppressive therapy, etc.

Using IDDM as an example, overt diabetes occurs when the level of glucose in the blood rises above a specific level, usually about 250 mg/dl. In humans a long presymptomatic period precedes the onset of diabetes. During this period there is a

gradual loss of pancreatic  $\beta$  cell function. The disease progression may be monitored in individuals diagnosed by family history and genetic analysis as being susceptible. The most important genetic effect is seen with genes of the major histocompatibility locus (IDDM1), although other loci, including the insulin gene region (IDDM2) also show linkage to the disease (see Davies et al, supra and Kennedy et al. (1995) Nature Genetics 9:293-298). Markers that may be evaluated during the presymptomatic stage are the presence of insulitis in the pancreas, the level and frequency of islet cell antibodies, islet cell surface antibodies, aberrant expression of Class II MHC molecules on pancreatic b cells, glucose concentration in the blood, and the plasma concentration of insulin. An increase in the number of T lymphocytes in the pancreas, islet cell antibodies and blood glucose is indicative of the disease, as is a decrease in insulin concentration. After the onset of overt diabetes, patients with residual  $\beta$  cell function, evidenced by the plasma persistence of insulin C- peptide, may also benefit from administration of the subject peptides in order to prevent further loss of function.

In multiple sclerosis, the overt disease is associated with muscle weakness, loss of abdominal reflexes, visual defects and paresthesias. During the presymptomatic period there is infiltration of leukocytes into the cerebrospinal fluid, inflammation and demyelination. Family histories and the presence of the HLA haplotype DRB1\*1501, DQA1\*0102, DQB1\*0602 are indicative of a susceptibility to the disease. Markers that may be monitored for disease progression are the presence of antibodies in the cerebrospinal fluid, "evoked potentials" seen by electroencephalography in the visual cortex and brainstem, and the presence of spinal cord defects by MRI or computerized tomography. Treatment during the early stages of the disease will slow down or arrest the further loss of neural function.

15

25

Rheumatoid arthritis is evidenced in the overt disease by severe inflammation and pain in the affected joints, produced by the malign growth of synovial cells. Virtually all patients have circulating titer of autoantibodies to the Fc region of IgG. Treatment with the subject peptides during early stages is desirable.

The host may be treated with one or several peptides chosen from the previously defined group. The choice of peptides from within the group may be empirically derived. An assay of particular interest for determining the choice of peptide will draw peripheral blood from the host, and determine whether a specific peptide inhibits the ability of the

CD8+ T lymphocytes to differentiate and lyse target cells. Such assays have been previously described (see Clayberger et al. [1993] Transplant. Proc. 25:477). The peptide(s) which demonstrate in vitro activity with a particular host will then be administered. It has been found that with particular genetic backgrounds, certain peptide sequences will not be active, as shown in the examples. Such peptides may have show in vivo activity in conjunction with other genetic backgrounds.

Peptides that are active with a number of different alleles are of particular interest. The screening assay may be performed with a number of different peripheral blood samples in order to determine whether the activity is maintained with cells of different haplotypes. The peptide(s) that demonstrate activity with a number of different hosts will be selected for use.

Desirably, the peptides should not induce an immune response, particularly an antibody response. Xenogeneic or mutated analogs of the native sequence may be screened for their ability provide a therapeutic effect without raising an immune response.

15

30

Various methods for administration may be employed. The peptide formulation may be given orally, or may be injected intravascularly, subcutaneously, peritoneally, etc. The dosage of the therapeutic formulation will vary widely, depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and the like. The initial dose may be larger, followed by smaller maintenance doses. For example, a dose of 1 to 100 mg peptide/kg body weight/week has been shown to be effective in delaying the onset of IDDM. For the treatment of IDDM, blood glucose will be monitored regularly to determine the efficacy of the treatment. The dose may be administered as infrequently as weekly or biweekly, or fractionated into smaller doses and administered daily, semi-weekly, etc. to maintain an effective dosage level of peptide. In many cases, oral administration will require a higher dose than if administered intravenously. The amide bonds, as well as the amino and carboxy termini, may be modified for greater stability on oral administration.

The subject peptides may be prepared as formulations at a pharmacologically effective dose in pharmaceutically acceptable media, for example normal saline, PBS, etc. The additives may include bactericidal agents, stabilizers, buffers, or the like. In order to enhance the half-life of the subject peptide or subject peptide conjugates, the peptides may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or another

conventional technique may be employed that provides for an extended lifetime of the peptides.

The peptides may be administered as a combination therapy with other pharmacologically active agents. The additional drugs may be administered separately or in conjunction with the peptide compositions, and may be formulated in the same formulation. Of particular interest are immunosuppressive agents, particularly those that are targeted to CD4<sup>+</sup> T lymphocytes, e.g. cyclosporins, FK-506, rapamycin, etc.

The following examples are offered by way of illustration and not by limitation.

10

### **EXAMPLES**

#### Delay of Onset of IDDM in NOD Mice following Administration of Peptides

Peptides: The following peptides, which have an amino acid sequence corresponding to a portion of the a-1 domain of MHC class I antigens, were synthesized by an automated peptide synthesizer using Fmoc chemistry. Peptides were purified by preparative reverse phase HPLC and shown to be greater than 95% homogeneous by analytical reverse phase HPLC. Amino acid content was confirmed by amino acid analysis. The peptide sequences are shown in Table 1. The class I MHC antigens of the NOD mouse, H-2K4 and H-2D5 are shown.

Table 1

20

		Corresponding allele	An	Amino acid residues							Reference		
			75	76	77	78	79	80	81	82	83	84	
	PEPTIDE 2702 (SEQ ID NO:4)	HLA-B2702	R	E	N	L	R	I	A	L	R	<b>Y</b>	1
;	PEPTIDE 07 (SEQ ID NO:7)	HLA-B7	R	E	s	L	R	N	L	R	G	Y	1
	PEPTIDE E (SEQ ID NO:8)	HLA-E	R	v	N	L	R	T	L	R	R	Y	2
)	PEPTIDE G (SEQ ID NO:11)	HLA-G	R	M	N	L	Ω	Ŧ	L	R	G	Y	3

30

25

	PEPTIDE K <sup>ts</sup> (SEQ ID NO:12)	H-2 K™	R	V	N	L	R	T	A	L	R	Y		4
	PEPTIDE K <sup>th</sup> (SEQ ID NO:13)	H-2 K**	R	v	s	L	R	T	A	L	R	Y		5
5	PEPTIDE D* (SEQ ID NO:14)	H-2 D*	R	V	D	. <b>L</b>	R	T	L	L	R	Y		5
	PEPTIDE K* (SEQ ID NO:9)	H-2 K	R	V	D	L	R	T	L	L	G	Y		6
10	PEPTIDE D <sup>b</sup> (SEQ ID NO:10)	H-2 D*	R	v	s	L	R	N	L	L	G	Y		5
	PEPTIDE K4 (SEQ ID NO:15)	H-2 K•	R	v	s	L	R	Ŧ	A	Q	R	Y		7

References: 1. Zemmour and Parham (1992) <u>Immunogenetics</u> 37:239.
 2. Koller et al. (1988) <u>J. Immunol.</u> 141:897.
 3. Heinrichs et al. (1990) <u>Immunol. Res.</u> 9:265.
 4. Minamide et al. (1988) <u>Immunogenetics</u> 27:148.
 5. Watts et al. (1987) J. Immunol. 139:3878.
 6. Reyes et al. (1982) <u>P.N.A.S.</u> 79:3270.
 7. Kabat, supra.

Treatment: In experiment I, 1 mg of PEPTIDE 07 (SEQ ID NO:7), 2702 (SEQ ID NO:4), E (SEQ ID NO:8) or G (SEQ ID NO:11) formulated in normal saline was administered intravenously once a week for a period of 8 weeks. All animals were 8 weeks old at the beginning of the experiment. In experiment II, 0.3 mg of PEPTIDE E (SEQ ID NO:8), D' (SEQ ID NO:10) or K (SEQ ID NO:9) were administered intraperitoneally three times a week until the onset of diabetes. All animals were five weeks old at the beginning of the experiment.

Determination of Blood Glucose: the blood glucose level in the blood of animals was determined once a week. 50 µl of blood from the tip of the tail was used for the blood glucose determination using a Johnson and Johnson glucose meter, according to the manufacturer's instructions. Animals with blood glucose levels greater than 250 mg/dl were considered to be diabetic.

30

35

Results: In experiment I, peptides were administered to 5 week old female NOD mice. The treatment was repeated weekly for a total of 8 weeks. 70% of control untreated female NOD mice developed diabetes by the age of 16 weeks. There was no statistically significant difference from the controls in animals that were treated with PEPTIDE 07 (SEQ ID NO:7), 2702 (SEQ ID NO:4) or G (SEQ ID NO:11). Animals that were treated with PEPTIDE E (SEQ ID NO:8) showed a significant delay in the onset of IDDM (p<0.03). Only 10% of the animals treated with PEPTIDE E (SEQ ID NO:8)

developed diabetes during the treatment period. After termination of treatment, 60% of the animals became diabetic by week 19. The data for experiment I is shown in Figure 1.

In experiment II, 0.3 mg of PEPTIDE E (SEQ ID NO:8), D<sup>b</sup> (SEQ ID NO:10) or K<sup>b</sup> (SEQ ID NO:9) was administered three times per week intraperitoneally. The mice were 5 weeks old at the beginning of the treatment period, and treatment was continued until the development of diabetes. Using this protocol, the delay of onset of diabetes with PEPTIDE E (SEQ ID NO:8) appeared to be less pronounced, but was still statistically significant. Even with this treatment, PEPTIDE K<sup>b</sup> (SEQ ID NO:9) significantly delayed the onset of diabetes. The data for experiment II is shown in Figure 2.

It is evident from the above results that peptides derived from a conserved region of the Class I MHC antigens can delay or prevent the onset of autoimmune disease. The subject methods provide a useful prophylaxis during the early stages of disease.

10

15

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

#### SEQUENCE LISTING

- (1) GENERAL INFORMATION:
  - (i) APPLICANT: SangStat Medical Corporation
- (ii) TITLE OF INVENTION: Treatment for Inhibiting the Progression of Autoimmune Disease
  - (iii) NUMBER OF SEQUENCES: 16
  - (iv) CORRESPONDENCE ADDRESS:
    - (A) ADDRESSEE: Flehr, Hohbach, Test, Albritton & Herbert (B) STREET: 4 Embarcadero Center, Suite 3400

    - (C) CITY: San Francisco
    - (D) STATE: CA
    - (E) COUNTRY: USA
    - (F) ZIP: 94111-4187
  - (v) COMPUTER READABLE FORM:
    - (A) MEDIUM TYPE: Floppy Disk
      - (B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS

      - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
  - (vi) CURRENT APPLICATION DATA:

    - (A) APPLICATION DATA:

      (A) APPLICATION NUMBER: PCT/US96/

      (B) FILING DATE: 05 APRIL 1996 (05.04.96)

      (C) CLASSIFICATION:
  - (viii) ATTORNEY/AGENT INFORMATION:

    - (A) NAME: Rowland, Bertram I.(B) REGISTRATION NUMBER: 20015
    - (C) REFERENCE/DOCKET NUMBER: FP-60130/BIR; SANG-29-PC
    - (ix) TELECOMMUNICATION INFORMATION:
      - (A) TELEPHONE: 415-494-8700 (B) TELEFAX: 415-494-8771
- (2) INFORMATION FOR SEQ ID NO:1:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 3 amino acids
      (B) TYPE: amino acid

    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Tyr Tyr Trp

- (2) INFORMATION FOR SEQ ID NO:2:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 4 amino acids
      (B) TYPE: amino acid

    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Arg Tyr Tyr Trp

- (2) INFORMATION FOR SEQ ID NO:3:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 14 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Arg Xaa Xaa Leu Arg Ile Xaa Leu Xaa Tyr Tyr Trp Xaa Ser

- (2) INFORMATION FOR SEQ ID NO:4:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Arg Glu Asn Leu Arg Ile Ala Leu Arg Tyr

- (2) INFORMATION FOR SEQ ID NO:5:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids (B) TYPE: amino acid

    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Arg Glu Asp Leu Arg Ile Ala Leu Arg Tyr

- (2) INFORMATION FOR SEQ ID NO:6:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Arg Glu Asn Leu Arg Ile Leu Leu Glu Tyr

(2) INFORMATION FOR SEQ ID NO:7:

#### WO 96/35443

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 10 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Arg Glu Ser Leu Arg Asn Leu Arg Gly Tyr 1 5 10

- (2) INFORMATION FOR SEQ ID NO:8:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 8 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Arg Val Asn Leu Arg Thr Leu Arg Arg Tyr 1 5 10

- (2) INFORMATION FOR SEQ ID NO:9:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Arg Val Asp Leu Arg Thr Leu Leu Gly Tyr 1 5 10

- (2) INFORMATION FOR SEQ ID NO:10:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Arg Val Ser Leu Arg Asn Leu Leu Gly Tyr

- (2) INFORMATION FOR SEQ ID NO:11:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr

- (2) INFORMATION FOR SEQ ID NO:12:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
      (B) TYPE: amino acid

    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Arg Val Asn Leu Arg Thr Ala Leu Arg Tyr 5

- (2) INFORMATION FOR SEQ ID NO:13:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids

    - (B) TYPE: amino acid
      (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13: Arg Val Ser Leu Arg Thr Ala Leu Arg Tyr
- (2) INFORMATION FOR SEQ ID NO:14:
  - (1) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Arg Val Asp Leu Arg Thr Leu Leu Arg Tyr

- (2) INFORMATION FOR SEQ ID NO:15:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
  - Arg Val Ser Leu Arg Thr Ala Gln Arg Tyr

- (2) INFORMATION FOR SEQ ID NO:16:

  - (i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 10 amino acids
    (B) TYPE: amino acid

    - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Arg Xaa Xaa Leu Arg Ile Xaa Leu Xaa Tyr

#### WHAT IS CLAIMED IS:

1. A method for affecting the course of an autoimmune disease involving T-cell mediated destruction of tissue, said method comprising:

administering to a mammalian host susceptible to said autoimmune disease, a peptide in an amount sufficient to modulate the activity of said T-cells; said peptide being an active sequence from about 6 to 22 amino acids in length and comprising the sequence:

aa<sup>70</sup> aa<sup>71</sup> Q aa<sup>73</sup> aa<sup>74</sup> R aa<sup>76</sup> aa<sup>71</sup> L aa<sup>79</sup> aa<sup>80</sup> aa<sup>81</sup> aa<sup>82</sup> aa<sup>83</sup> aa<sup>84</sup> aa<sup>85</sup> aa<sup>86</sup> aa<sup>87</sup> aa<sup>86</sup> aa<sup>87</sup> aa<sup>86</sup> aa<sup>87</sup> aa<sup>88</sup> aa<sup></sup>

Wherein:

aa70 is Q, H, S, N or K;

aa" is an aliphatic neutral amino acid, including S, A and T;

aan is T or A;

aa" is D, Y or H;

aa76 is E or V;

aa<sup>n</sup> is D, S or N;

15 aa\*\* is R or G;

aa is T, I, N or an aromatic amino acid, e.g., F, W or Y;

aa<sup>81</sup> is an aliphatic non-polar amino acid including L or A;

aam is R, L or an aromatic amino acid, particularly L;

aas is G or R;

20 aas is W or N;

aa" is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S;

aa<sup>38</sup> is an aromatic amino acid or aliphatic amino acid of from 5 to 6 carbon atoms, particularly F, W, Y, L, I or V;

25 aa<sup>20</sup> is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S;

aa∞ is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N, Q, F, W, or Y, more particularly, A, W, F, N, Q, or S; and

aa<sup>91</sup> is any amino acid, particularly neutral aliphatic or aromatic, G, A, S, T, M, N,

Q, F, W, or Y, more particularly, A, W, F, N, Q, or S;

wherein the course of said autoimmune disease is affected.

2. A method according to Claim 1, wherein said peptide is at least about 10 amino acids, and comprises the sequence (SEQ ID NO:3) R V/E N/D L R I A/L L R/E Y Y W Q/D S.

- 5 3. A method according to Claim 2, wherein said peptide is dimerized.
  - 4. A method according to Claim 2, wherein said peptide comprises at least one D-isomer amino acid.
- A method according to Claim 2, wherein said autoimmune disease is insulin dependent diabetes mellitus.
  - 6. A method according to Claim 5, wherein said administering is during the preclinical stage of said insulin dependent diabetes mellitus.

15

7. A method according to Claim 6, wherein said peptide is selected from the group consisting of: (SEQ ID NO:1) RENLRIALRY; (SEQ ID NO:2) REDLRIALRY; (SEQ ID NO:3) RENLRILLEY; (SEQ ID NO:4) RESLRNLRGY; (SEQ ID NO:5) RVNLRTLRRY; (SEQ ID NO:6) RVDLRTLLGY; and (SEQ ID NO:7) RVSLRNLLGY.

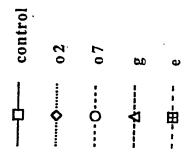
20

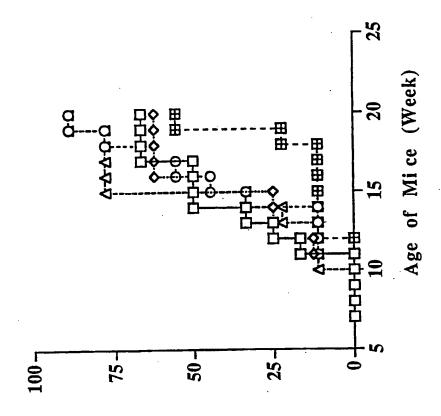
8. A method for inhibiting the course of insulin dependent diabetes mellitus (IDDM), said method comprising:

administering to a mammalian host susceptible to said IDDM, a peptide selected from the group consisting of: (SEQ ID NO:1) RENLRIALRY; (SEQ ID NO:2)

REDLRIALRY; (SEQ ID NO:3) RENLRILLEY; (SEQ ID NO:4) RESLRNLRGY; (SEQ ID NO:5) RVNLRTLRRY; (SEQ ID NO:6) RVDLRTLLGY; and (SEQ ID NO:7) RVSLRNLLGY;

wherein the course of said IDDM is inhibited.





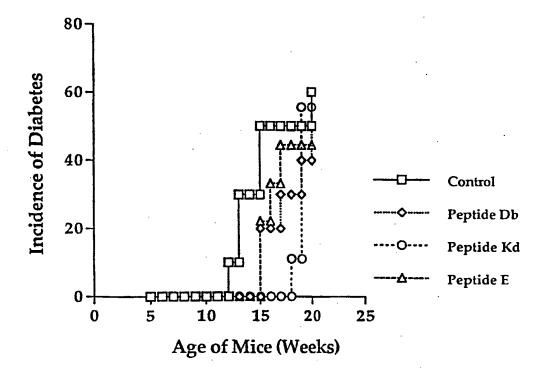
Incidence of Diabetes (%)

FIGURE 1

SUBSTITUTE SHEET (RULE 26)

2/2 .

# FIGURE 2



# SUBSTITUTE SHEET (RULE 26)

# INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/04710

A. CLASSIFICATION OF SUBJECT MATTER PCR(6) - Asik 3200, 3302, COX 500, 700, 1700. US CL514/13, 14, 15, 16, 17; 530735, 327, 328, 329, 330. According to International Paient Classification system followed by classification and IPC  B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols)  U.S. : 514/13, 14, 15, 16, 17; 5307326, 227, 328, 329, 330.  Decumentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Clastion of document, with indication, where appropriate, of the relevant passages  Y. WO, A., 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A., 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allogarif Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1  Antigen", pages 297-307, especially page 303.  Purcher document serious serious are distinct on the art which is not considered to the substitution cause to septide the publication of the international search  The observation of clade documents are substituted that the international search profit face shadow."  The observation of clade documents are substituted to the international search profit date of the actual completion of the international search profit date of the actual completion of the international search profit date of the actual completion of the international search profit date of the actual com		· · · · · · · · · · · · · · · · · · ·								
APS, CAS ONLINE, MEDIUNE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY) OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class- 1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1  Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  ** Special extegories of isolated commonia.  ** Special extegories of isolated commonia.  ** Further documents are listed in the continuation of Box C.  ** Special extegories of isolated commonia.  ** Special extegories of isolated commonia.  ** Special extegories of isolated commonia.  ** Accommendation of the Commonia starch to the relevant passage Relevant to claim No.  ** Special extegories of isolated commonia.  ** Accommendation of the Commonia starch to the relevant passage Relevant to claim No.  ** Special extegories of isolated commonia.  ** Accommendation of the Commonia starch to the relevant passage Relevant to claim No.  ** Special extegories of isolated commonia.  ** Accommendation of the continuation of Box C.  ** Special extegories of isolated commonia.  ** Accommendation of the continuation of Box C.  ** Special extegories of isolated commonia.  ** Accommendation of the continuation of Box C.  ** Special extegories of isolated commonia.  ** Accommendation of the continuation of the continuation of Box C.  ** Special extegories of isolated commonia.  ** Accommendation of the continuation of the continuation of the										
According to International Patent Classification (IPC) or to both national classification and IPC  B. FIELDS SEARCHED  Minimum documentation searched (classification system followed by classification symbols)  U.S.: 514/13, 14, 15, 16, 17; 530/326, 327, 328, 329, 330.  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  Y WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1  Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C. See patent family annex.  * Special outgeries of clied documental.  To document-family the previous of the set visicle is not considered to be of practical relevance to the client which my three decises on priority principle or theory underlying the investion cannot be operated and the second of the set visicle is not considered to be of practical relevance, the chained diversion cannot be operated underlying the investion cannot be septiment which my three decises on priority principle or theory underlying the investion cannot be operated underlying the investion cannot be operated underlying the investion cannot be ope	IPC(6) :A61K 38/00, 38/02; C07K 5/00, 7/00, 17/00.									
B. FIELDS SEARCHED  Minimum documentation searched (classification system followed by classification symbols)  U.S.: 514/13, 14, 15, 16, 17; 530/326, 327, 328, 329, 330.  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched letter than minimum documentation to the extent that such documents are included in the fields searched letter than minimum documentation to the extent that such documents are included in the fields searched letteronic data base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  P. Cale Cale Consideration of the search of the relevant passages  Relevant to claim No.  Y. WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C. See patent family annex.  ** Special categories of iclaid documents:  ** Special categories of iclaid documents:  ** Special categories of iclaid documents:  ** Additional designation of iclaid documents:  ** Category*  ** Special categories of iclaid documents:  ** Additional designation of include on a refer the international filing date iclaid on the international search to be of paticular reference; the chiender investion ensured to be of pat	US CL :514/13, 14, 15, 16, 17; 530/326, 327, 328, 329, 330.  According to International Patent Classification (IPC) or to both pational classification and IPC									
Minimum documentation searched (classification system followed by classification symbols)  U.S.: \$14/13, 14, 15, 16, 17; \$30/326, 327, 328, 329, 330.  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched expenditure of the provided in the fields searched that base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  Y. WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A, 93/17699 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents sited in the continuation of Box C. See patent family annex.  **  **  **  **  **  **  **  **  **										
U.S. 514/13, 14, 15, 16, 17; 530/326, 327, 328, 329, 330.  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched extended that have consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Y. WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C. See patent family sunnex.  * Special citypric of clast documence:  * Special citypric of clast documen			d by classification symbols)							
Decumentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y. Journal of Immunology, Volume 152, issued 1994, Nisco et al., "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Purchar documents are listed in the continuation of Box C. See patent family annex.  **Special categories of clad documents:  **A document reforming the general state of the art which is not considered to involve relations to the publication date of unifier clustice or other special reason to specifical search to a published of the set of the state of the publication date of unifier clustice or other special reason to special reas				Ì						
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  APS, CAS ONLINE, MEDLINE, BIOSIS  C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y. WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y. Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C. See patent family annex.  ** Special categories of cited documents:  ** Special ca	0.3.	314/13, 14, 13, 16, 17, 336/326, 327, 326, 327, 336	·							
C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special eutreprice of clear documents which have the international filing date or priority date cleaned which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an o	Documentat	ion searched other than minimum documentation to the	extent that such documents are included	in the fields searched						
C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special eutreprice of clear documents which have the international filing date or priority date cleaned which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an o										
C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special eutreprice of clear documents which have the international filing date or priority date cleaned which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement which may throw doubt on priority claimfor or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an oral disclosure, use, stabiblion or other special reason (as specified)  To decement referring to an o										
C. DOCUMENTS CONSIDERED TO BE RELEVANT  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  Y WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special autgerirs of clead documents.  * Special autgerirs of clead documents.  * To document which here the international filing date to be of particular relevance: the claim of the art which is not considered to be of particular relevance.  * Special autgerirs of clead documents are particulated on or after the international filing date or priority date claimed in received to be of particular relevance.  * Special autgerirs of clead documents which here the international filing date or priority date claimed to a considered to be of particular relevance.  * Special autgerirs of clead documents which is not considered to be of particular relevance.  * Special autgerirs of clead documents which here the international filing date or other special reason (as specified)  * To document which here the international filing date which is not considered to be of particular relevance; the claimed invention cannot be considered or or constant be considered or or constant be considered or constant by a priority date claimed invention cannot be considered or constant by a priority date claimed invention and the constant which here are on other special elevance; the claimed inve	Electronic d	lata base consulted during the international search (na	ime of data base and, where practicable	, search terms used)						
Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  **To document which may throw doubts on piority chain(b) or which is cited occument published relevance to other relevance to other themselved to involve an investive representation of the desired prior to the international fling date but hater than the priority date submit on the priority date to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered over or cannot be considered to involve an investigation that of the work of the surface	APS, CA	S ONLINE, MEDLINE, BIOSIS								
Category*  Citation of document, with indication, where appropriate, of the relevant passages  WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  **To document which may throw doubts on piority chain(b) or which is cited occument published relevance to other relevance to other themselved to involve an investive representation of the desired prior to the international fling date but hater than the priority date submit on the priority date to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered to involve an investive representation of the comment of practicular relevance: the chained investion cannot be considered over or cannot be considered over or cannot be considered to involve an investigation that of the work of the surface										
WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special categories of clied documents:  ** Special categori	C. DOC	UMENTS CONSIDERED TO BE RELEVANT								
WO, A, 93/17699 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Purther documents are listed in the continuation of Box C.  * Special categories of cited documents:  A Special categories of cited documents:  A Special categories of cited documents:  A Special categories of cited documents with may throw doubts on priority classical or which is cited to stabilish the publication size of sunder citation or other special reason (as specified)  To document which may throw doubts on priority classical or other means.  The document which may throw doubts on priority classical or which is cited to stabilish the publication size of sunder citation or other special reason (as specified)  To document which may throw doubts on priority classical or which is cited to stabilish the publication size of sunder citation or other special reason (as specified)  To document which may throw doubts on priority classical or a special reason (as specified)  To document which may throw doubts on priority classical or a special reason (as specified)  To document which may throw doubts on priority classical in a sometime of paticular releasons; the chained investion cannot be considered to a sometime of the same paticular through the substance of paticular releasons; the chained investion cannot be considered and with one or marce other such documents, such combination with one or marce other such documents, such combination being obvious as investive rap when the documents is	Category*	Citation of document with indication where ar	portopriate, of the relevant passages	Relevant to claim No.						
LELAND STANFORD JUNIOR UNIVERSITY) 16 September 1993, see entire document.  Y WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  * Special categories of cited documents:  A' document defining the general state of the ant which is not considered to be of publication references  E' cartier document published on or after the international filing date or other special reason (as specified)  11 document which may throw doubts on priority chisin(b) or which is cited to establish the publication date of another citation or other special reason (as specified)  2* document published prior to the international filing date but better than the priority date claimed investion cannot be considered to involve an investive step when the document is such about the document is econical document of puricular relevance; the claimed investion cannot be considered to involve an investive step when the document is such about the document is such about the priority date claimed.  To document published prior to the international filing date but their than the priority date claimed investion cannot be considered to involve an investive step when the document is such about the priority date claimed investion cannot be considered to involve an investive step when the document is such about the considered to involve an investive step when the document is such about the considered to involve an investive step when the document is such about the considered to involve an investive step when the document is such about the prior	Category	Citation of document, was marenos, where of								
1993, see entire document.  Y WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.    Further documents are listed in the continuation of Box C.   See patent family annex.  * Special categories of cited documents:  * Comments of particular relevance; the claimed invention cannot be considered to be observed an inventive reproduction cannot be considered to involve an inventive reproduction cannot be considered to involve an inventive reproduction of the considered to the considered to involve an inventive reproduction of the considered to involve an inventive reproduction of the considered to the considered to the considered to the considered to the conside	Υ	WO, A, 93/17699 (THE BOARD	OF TRUSTEES OF THE	1-8						
WO, A, 90/10016 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 07 September 1990, see entire document.  Y Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Y Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.    Further documents are listed in the continuation of Box C.   See patent family annex.		LELAND STANFORD JUNIOR UN	IVERSITY) 16 September							
CALIFORNIA) 07 September 1990, see entire document.  Y		1993, see entire document.								
CALIFORNIA) 07 September 1990, see entire document.  Y										
Journal of Immunology, Volume 152, issued 1994, Nisco et al, "Induction of Allograft Tolerance in Rats by an HLA Class-1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  Further document sare listed in the continuation of Box C.  See patent family annex.  The document defining the general state of the art which is not considered to be of pericular relevance to be of pericular relevance.  The cartier document published on or after the international filing date to easily the published of atte of another criation or other special reason (as specified)  To document referring to an oral disclosure, use, exhibition or other means  The document published prior to the international filing date but later than the priority date claimed invention cannot be considered on inventive step when the document is necessive step when the document is necessive step when the document is necessary of the asset patent family  Date of the actual completion of the international search  To document published prior to the international filing date but later than the priority date claimed  To document published prior to the international filing date but later than the priority date claimed  To document published prior to the international search  To document referring to an oral disclosure, use, exhibition or other means  To document published prior to the international filing date but later than the priority date claimed  To document published prior to the international filing date but later than the priority date claimed  To document published prior to the international search  To document published prior to the international filing date but later than the document is naken along the considered to involve an inventive	Υ			1-8						
al, "Induction of Allograft Tolerance in Rats by an HLA Class- 1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  To document published after the international filing date or priority date and not inconflict with the application but cited to medicate and the publication of the cited to actabilith the publication and act of another chainles or other special reason (as apostal reason (as apostal) areason (as apostal)		CALIFORNIA) 07 September 1990	, see entire document.	·						
al, "Induction of Allograft Tolerance in Rats by an HLA Class- 1-Derived Peptide and Cyclosporine A", pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  To document published after the international filing date or priority date and not inconflict with the application but cited to medicate and the publication of the cited to actabilith the publication and act of another chainles or other special reason (as apostal reason (as apostal) areason (as apostal)	,	Investigation Volume 1	E2 included 1994 Niggo of	1_0						
1-Derived Peptide and Cyclosporine A**, pages 3786-3792, especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen*, pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  Special categories of cited documents:  'A' document defining the general state of the art which is not considered to be of particular relevance:  'E' cartier document published on or after the international filing date or priority date and not inconflict with the application but cited to understand the priority date of an acutal reason (as apposition) or other special reason (as aposition)  'C' document published of priority claim(t) or which is cited to establish the publication date of another citation or other special reason (as aposition)  'O' document efferring to an oral disclosure, use, exhibition or other means  'P' decument published after the international filing date but hater than the priority date of another citation or other means  'A' document published after the international filing date or priority date and not application but cited to understand the principle or theory relieving the furvaction cannot be considered above for cannot be considered to visolve an investive step when the document is taken alone of particular relevance; the claimed invention cannot be considered to involve an investive step when the document is combined with one or more other such document be considered to involve an investive step when the document is combined with one or more other such document be considered to involve an investive step when the document be considered to involve an investive step when the document be considered to involve an investive step when the document is combined with one or more other such document section to considered to involve an investive step when the document is combined with one or more other such document section to consider and to inv	Y			1-6						
especially page 3787.  Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  Special categories of cited documents:  A document defaining the general state of the art which is not considered to be of particular relevance to be of particular relevance of cited to establish the publication date of another citation or other special reason (as specified)  Code document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  Code document velocity from the international filing date but hater than the document which is inventive step when the document is enabled from the international filing date but hater than the document which is inventive step when the document is enabled from the international filing date but hater than the document when the document is enabled from the international filing date but hater than the document when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is enabled to involve an inventive step when the document is ena			-							
Cell, Volume 62, issued 27 July 1990, Stagsted et al, "Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  See patent family annex.  To document defining the general state of the art which is not considered to be of particular relevance  To document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another chalion or other special reason (as specified)  To document referring to an oral disclosure, use, exhibition or other means  To document published prior to the international filing date but later than the comment referring to an oral disclosure, use, exhibition or other means  The document published prior to the international filing date but later than the comment priority date chained  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks  Box PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196		•	· pages 0/00 0/02,							
"Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  Special categories of clied documents:  A document defining the general state of the art which is not considered to be of particular relevance in the international filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone of the actual completion of the international filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed invention cannot be considered to involve an inventive step when the document is accombined with one or more others such documents, such combinations being obvious to a person skilled in the sat documents. Such combinations being obvious to a person skilled in the sat documents. Such combinations are combined to the same patient family.  Authorized officer  Authorized officer  AVIS M. DAVENPORT  T anticular relevan		copositiny page 5727.								
"Regulation of Insulin Receptor Functions by a Peptide Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  Special categories of clied documents:  A document defining the general state of the art which is not considered to be of particular relevance in the international filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone of the actual completion of the international filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed inventional filing date but later than the priority date claimed invention cannot be considered to involve an inventive step when the document is accombined with one or more others such documents, such combinations being obvious to a person skilled in the sat documents. Such combinations being obvious to a person skilled in the sat documents. Such combinations are combined to the same patient family.  Authorized officer  Authorized officer  AVIS M. DAVENPORT  T anticular relevan	Υ	Cell, Volume 62, issued 27 Jul	y 1990, Stagsted et al,	1-8						
Derived from a Major Histocompatibility Complex Class 1 Antigen", pages 297-307, especially page 303.  Further documents are listed in the continuation of Box C.  Special categories of cited documents:  'A' document defiaing the general state of the art which is not considered to be of particular relevance to be of particular relevance to earlier document published on or after the international filing date  'E' cartier document published on or after the international filing date  'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  'O' document referring to an oral disclosure, use, exhibition or other means  'P' document published prior to the international filing date but later than the priority date chained  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks BOX PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196										
Further documents are listed in the continuation of Box C.  Special categories of cited documents:  A comment defining the general state of the art which is not considered to be of particular relevance  E cartier document published on or after the international filing date  L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  O document referring to an oral disclosure, use, exhibition or other means  P document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  T inter document published after the internation of Box C.  See patent family annex.  T inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention connot be considered novel or cannot be considered to involve an inventive step when the document is atken alone  "X"  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered to involve an inventive step when the document is considered to involve an inventive step when the document is considered to involve an inventive step when the document is considered to involve an inventive step when the document is considered to involve an inventive step when the document is considered novel or cannot be considered novel or c										
Special categories of cited documents:  A* document defining the general state of the art which is not considered to be of particular relevance  B**E* earlier document published on or after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document published prior to the international filing date but later than the priority date chained  B**Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196		Antigen", pages 297-307, especia	ally page 303.	·						
Special categories of cited documents:  A* document defining the general state of the art which is not considered to be of particular relevance  B**E* earlier document published on or after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document published prior to the international filing date but later than the priority date chained  B**Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196		,								
Special categories of cited documents:  A* document defining the general state of the art which is not considered to be of particular relevance  B**E* earlier document published on or after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document referring to an oral disclosure, use, exhibition or other means  B**C** document published prior to the international filing date but later than the priority date chained  B**Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196										
*A* document defining the general state of the art which is not considered to be of particular relevance  *B* cartier document published on or after the international filing date  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  *O* document referring to an oral disclosure, use, exhibition or other means  *P* document published prior to the international filing date but later than the priority date claimed  *Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Box PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  *Authorized officer  AVIS M. DAVENPORT  document defining the general state to involve an invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone  ***  document referring to an oral disclosure, use, exhibition or other means  ***  document published prior to the international filing date but later than the priority date claimed invention cannot be considered to involve an inventive step when the document is taken alone  ***  document referring to an oral disclosure, use, exhibition or other another claimed invention cannot be cons	Furth	er documents are listed in the continuation of Box C	. See patent family annex.							
'A' document defining the general state of the art which is not considered to be of particular relevance  'E' earlier document published on or after the international filing date considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is fact alone of document referring to an oral disclosure, use, exhibition or other means  'P' document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Preservable international search stream to be of outsidered novel or cannot be considered to involve an inventive step when the document is combined into invention cannot be considered novel or cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered novel or cannot be consi	• Sp	ccial categories of cited documents:	"T" Inter document published after the inte	emutional filing date or priority						
*2" cartier document published on or after the international riting date  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230  Comsidered novel or cannot be considered to involve an inventive step when the document is taken alone  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone  document is taken alone  To when the document is taken alone  or another considered to involve an inventive step when the document is taken alone  To wh			principle or theory underlying the inv	ention						
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another cination or other special reason (as specified)  *O* document referring to an oral disclosure, use, exhibition or other means  *P* document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  when the document is taken alone  document is taken alone  *V*  document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  document member of the same patent family  Date of mailing of the international search report  Authorized officer  AVIS M. DAVENPORT  AVIS M. DAVENPORT  Telephone No. (703) 308-0196			"X" document of particular relevance; the	e claimed invention cannot be red to involve an inventive step						
special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks  Rox PCT  Washington, D.C. 20231  Facsimile No. (703) 305-3230  Telephone No. (703) 308-0196	L do	current which may throw doubts on priority claim(s) or which is								
**O* document referring to an oral disclosure, use, exhibition or other means  "P* document published prior to the international filing date but later than the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230  Combined with one or more other such documents, such combination being obvious to a person skilled in the art  document member of the same patent family  document member of the same patent family  Authorized officer  AVIS M. DAVENPORT  AVIS M. DAVENPORT  Telephone No. (703) 308-0196	spe	en an communa and handerman some or another cummon of other	considered to involve an inventive	step when the document is						
the priority date claimed  Date of the actual completion of the international search  11 JULY 1996  Date of mailing of the international search  25 JUL 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230  Date of mailing of the international search  Authorized officer  AVIS M. DAVENPORT  Telephone No. (703) 308-0196			combined with one or more other suc	h documents, such combination						
Date of the actual completion of the international search  11 JULY 1996  25 JUL 1996  Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230  Date of mailing of the international search report  Authorized officer  AVIS M. DAVENPORT  Telephone No. (703) 308-0196	*P* document published prior to the international filing date but later than *&* document member of the same patent family the priority date claimed									
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Pacsimile No. (703) 305-3230  Authorized officer  AVIS M. DAVENPORT  Telephone No. (703) 308-0196	<del></del>									
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Pacsimile No. (703) 305-3230 AVIS M. DAVENPORT Telephone No. (703) 308-0196	11 JULY 1996 <b>25</b> JUL 1996									
Box PCT Washington, D.C. 20231  Pacsimile No. (703) 305-3230  AVIS M. DAVENPORT  Telephone No. (703) 308-0196										
Washington, D.C. 20231 Pacsimile No. (703) 305-3230 Telephone No. (703) 308-0196	Box PCT		AVIS M. DAVENPORT	rotas,						
	Washington	Washington, D.C. 20231								

THIS PAGE BLANK (USPTO)